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Mini-Review

Immunizations for HIV-infected people

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ABSTRACT

Vaccines are critical components for protecting HIV-infected adults from an increasing number of preventable diseases. However, missed opportunities for vaccination among HIV-infected persons persist, likely due to concerns regarding the safety and efficacy of vaccines, as well as the changing nature of vaccine guidelines. In addition, the optimal timing of vaccination among HIV-infected adults with regard to HIV stage and receipt of antiretroviral therapy remain an important question. This article provides a review of the current recommendations regarding vaccines among HIV-infected adults and a comprehensive summary of the evidence-based literature of the benefits and risks of vaccines among this vulnerable population.

KEYWORDS: HIV, vaccination, immunosupression, antiretroviral therapy, immunization

INTRODUCTION

Providing appropriate immunizations is an important component of comprehensive HIV clinical care. The Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for routine immunizations of adults, including specific recommendations for HIV-infected adults [1]. In addition, the US Guidelines for the Prevention and Treatment of Opportunistic Infections and the Infectious Diseases Society of America also provides specific vaccine recommendations for HIV-infected adults [2, 3]. The major immunizations indicated for HIV-infected adults are summarized in figure 1. Immunizing HIV-infected persons poses several challenges and concerns related to efficacy and safety. Unfortunately, HIV-infected persons with current or past advanced immunosuppression often have suboptimal responses to recommended vaccines [4, 5, 6, 7, 8]. In general, responses to immunization are better when the vaccine is given as early as possible in the course of HIV infection. From a safety standpoint, HIV-infected persons with advanced immunosuppression have the potential for life-threatening complications if they receive a live vaccine. Of lesser concern, early studies suggested that immune stimulation produced by vaccination resulted in a burst in HIV replication [9] but follow-up studies have shown increases in HIV RNA levels following vaccination are transient and clinically insignificant [10].

Importance of vaccinations for HIV patients

Vaccinations are particulary important for HIV-infected adults. Due to impaired host defenses, HIV-infected persons have both an increased risk and severity of vaccine-preventable infections. For example, HIV-infected persons have a markedly higher risk of invasive pneumococcal disease despite the advent of combination antiretroviral therapy (CART). Similarly, infection with the hepatitis B virus (HBV) is more likely to progress to cirrhosis and hepatocellular cancer among HIV-infected persons compared with HIV-uninfected persons. In addition to immunologic reasons, HIV-infected persons are at higher risk due to frequent contact with the medical environment and shared routes of transmission with infectious pathogens such as HBV and human papillomavirus (HPV).

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Vaccine	Recommendation and Comment
Pneumococcal (polysaccharide)	Recommended. Combined conjugate and polysaccharide series.
Tetanus, diptheria, pertussis (Td/Tdap)	Recommended. Substitute 1 dose of Tdap for Td booster, then boost with Td every 10 years.
Meningococcal	Recommended if some other risk factor is present. Meningococcal conjugate vaccine preferred (for adults aged < 55).
Influenza (inactivated)	Recommended. Vaccinate annually. Avoid live attenuated intranasal influenza vaccine.
Hepatitis A	Recommended for HAV non-immune persons with indication.
Hepatitis B	Recommended for all HBV non-immune individuals.
Human papillomavirus (HPV)	Recommended for all females through age 26 (HPV4 and HPV2); Recommended for all males age 9 to 26 (HPV4 only).
Mumps, Measles, Rubella (MMR)	Contraindicated when CD4 count < 200 cells/mm^3. Recommended in patients with CD4 count ≥ 200 cells/mm^3 if non-immune.
Varicella	Contraindicated when CD4 < 200 cells/mm^3. Consider if CD4 count ≥ 200 cells/mm^3 and person non-immune to varicella.
Zoster	Contraindicated in patients with CD4 < 200 cells/mm^3. No recommendation for or against if CD4 ≥ 200 cells/mm^3.

Figure 1. Recommended immunizations for HIV-infected adults.

Pneumococcal vaccine

Persons infected with HIV have an increased risk of developing invasive disease with *Streptococcus pneumoniae* infection [11]. Observational and placebo-controlled trials have shown conflicting results for the effectiveness of the 23-valent polysaccharide pneumococcal vaccination (PPSV23; *Pneumovax 23*) in HIV-infected adults [12, 13]. Nevertheless, ACIP and US Guidelines for the Prevention and Treatment of Opportunistic Infections have historically recommended that all HIV-infected adults receive the 23-valent polysaccharide pneumococcal vaccine. In June 2012, the ACIP issued a new recommendation to utilize both the conjugate 13-valent (PCV13; *Prevnar 13*) pneumococcal vaccine and the 23-valent polysaccharide pneumococcal vaccine in immunocompromised adults, including HIV-infected persons (Figure 2) [14]. Pneumococcal vaccine-naïve persons should receive the PCV13 vaccine first, followed by a dose of PPSV23 at least 8 weeks later for adults aged 19 to 64 (or 6 to 12 months later after PCV13 for adults 65 years or older); a second dose of PPSV23 should be given 5 years later. Individuals who have previously received PPSV23 vaccination should receive PCV13, but not within 1 year of receiving a dose of the PPSV23 vaccine. In this situation, if the patient had received only one prior dose of PPSV23, they should receive a second dose of PPSV23 at least 8 weeks after the PCV13 dose and at least 5 years after the prior PPSV23 dose. In all situations, patients who have received PPSV23 prior to age 65 should receive one additional dose of PPSV23 at age 65, or later if their last dose of PPSV23 was given within the prior 5 years. Initial vaccination should be given as early in the course of HIV infection as possible, preferably before the CD4 count increase to less than 200 cells/mm. If a patient has a CD4 count less than 200 cells/mm and not on antiretroviral therapy, many experts would recommend deferring pneumococcal immunization until the patient starts an antiretroviral therapy, suppresses HIV RNA levels, and has improvement in immune function. The widespread use of the conjugate pneumococcal vaccines in children has resulted in a significant decline in the rates of invasive pneumococcal disease in adults [15]. A randomized, placebo-controlled trial of PCV13 in 85,000 Dutch adults without HIV infection aged 65 years or older showed 45.6% efficacy against vaccine-type pneumococcal pneumonia and 75.0% efficacy against vaccine-type invasive pneumococcal disease [16].

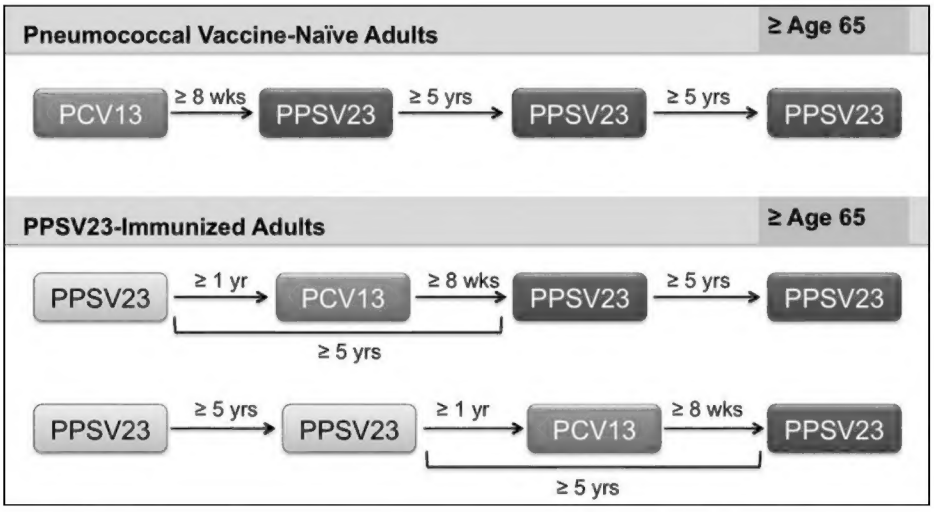


Figure 2. Pneumococcal immunization in immunocompromised adults.

Tetanus, diphtheria, and pertussis (Tdap) vaccine

Routine immunization with the tetanus and diphtheria toxoid vaccine (Td) is recommended for all HIV-infected adults. This toxoid vaccine uses neutralized *Clostridium tetani* and *Corynebacterium diphtheriae* toxins. Two Tdap vaccines are approved by the FDA: *Boostrix* (for persons aged 10 and older) and *Adacel* (for persons aged 11 to 64) [17]. The recommended ACIP standard practices for primary immunization and updating immunity against tetanus and diphtheria among HIV-infected persons are the same as those for the general population. Adults who have never been vaccinated against tetanus, diphtheria, or pertussis (or who have unknown immunization status) should receive a full series (three injections that contain the tetanus and diphtheria toxoids). Preferably, the first dose in the series should consist of Tdap, and the remaining two Td, but Tdap can substitute for any one of the Td doses in the series. The first two doses should be given at least 4 weeks apart and the third dose should be given 6 to 12 months after the second dose. Adults with incomplete history of completing a primary vaccination series should receive the remaining doses. To maintain immunity, the Td should be administered as a booster every 10 years, with the exception that adults aged 19 to 64 (and those 65 and older who anticipate contact with children aged 12 months or younger) should receive a single dose of Tdap to replace their next dose of Td if they have not previously received the Tdap vaccine. Intervals less than 10 years since the prior Td may be used for giving Tdap to specifically protect against pertussis, especially in persons at increased risk for acquiring pertussis or developing pertussis-associated complications [17].

Haemophilus influenzae type b (Hib) vaccine

Although preventing invasive *Haemophilus influenzae* type B infections remains an important concern for HIV-infected children, there is no evidence that invasive *H. influenzae type B* infections occur at a higher rate in HIV-infected adults. Administering *H. influenzae type b* (Hib) vaccine (*HibTITER, ActHIB*, and *PedvaxHIB*) is not recommended for HIV-infected adults because there are no efficacy data to base such a recommendation.

Meningococcal vaccine

Infection with HIV is not considered a high-risk condition for developing invasive infection caused by *Neisseria meningitidis*. Currently available meningococcal vaccines consist of the tetravalent polysaccharide vaccine (MPSV4) (*Menomune*) and the tetravalent polysaccharide-protein conjugate vaccines (MCV4) (*Menactra* and *Menveo*) [18]. Both vaccines contain the serotypes A, C, Y, and W-135 [18]. The MCV4 vaccines are preferred

over the polysaccharide vaccine, but the MPSV4 is considered an acceptable alternative. For HIV-infected adults, meningococcal vaccine is not routinely recommended, but it is safe to give when an indication is present. The following adult populations have a specific indication to receive meningococcal vaccine: persons with anatomical or functional asplenia, persons with terminal complement deficiency, first-year college students living in dormitories, military recruits, microbiologists routinely exposed to *N. meningitidis,* and persons travelling to a hyperendemic region. In addition, the MCV4 vaccine is now recommended routinely for all children at age 11 to 12 and for unvaccinated adolescents at high school entry [18]. In late 2014, a group B meningococcal vaccine (*Trumemba*) received FDA approval to prevent invasive type b disease in persons aged 10 to 25. This vaccine has been studied in health individuals [19] and there are no specific recommendations for the use of group B meningococcal vaccine in HIV-infected persons.

Influenza vaccine

Current ACIP and DHHS guidelines recommend annual administration of inactivated trivalent influenza virus vaccine for all HIV-infected persons, regardless of CD4 count [20]. Although only a few data exist regarding the frequency and severity of influenza illness in HIV-infected persons, available data suggest that complications from influenza are probably higher in HIV-infected persons, particularly those patients with AIDS [20, 21]. Influenza vaccination reduces respiratory symptoms and documented influenza illness among HIV-infected adults. Patients with low CD4 counts often have suboptimal antibody responses to influenza vaccination. The live attenuated intranasal influenza vaccine (*Flumist)* is contraindicated for HIV-infected persons, but not their household contacts.

Hepatitis A virus vaccine

Hepatitis A vaccination is recommended for HIV-infected persons who are seronegative for hepatitis A virus and who have medical, behavioral, or occupational indications. Medical indications consist of clotting-factor disorders or chronic liver disease, including chronic hepatitis B or C virus infection. Behavioral indications include use of injection drugs and men who have sex with men. In addition, persons with planned travel to countries that have high or intermediate endemicity for hepatitis A virus (Figure 3) should receive hepatitis A vaccine prior to travel. Occupational indications include work with hepatitis A in research laboratories or hepatitis A-infected primates. Patients should receive 2 doses of hepatitis A vaccine (*Havrix or Vaqta*) given at least 6 months apart (Figure 4) [22]. Hepatitis A vaccine has been shown to be safe and effective in most HIV-infected persons [23] although several studies have shown reduced responses to hepatitis A vaccine among HIV-infected persons who have a CD4 count less than 200 to 300 cells/mm [24]. Although these suboptimal vaccine responses would suggest a need for checking a post-vaccination titer, the ACIP guidelines do not recommend routine testing for antibody to hepatitis A following vaccination.

Hepatitis B virus vaccine

Persons infected with HIV who acquire hepatitis B virus are more likely to have acute symptomatic hepatitis B virus infection and to develop chronic active hepatitis B virus infection [25, 26]. Current guidelines recommend hepatitis B virus vaccination for all persons infected with HIV who do not have serologic evidence of prior infection with hepatitis B virus [27]. The 2015 ACIP vaccine guidelines recommend immunocompromised adult patients receive 40 mcg of hepatitis B surface antigen with each scheduled vaccine dose for both *Engerix-B* and *Recombivax-HB,* whereas the 2013 guidelines recommend 20 mcg per dose with *Engerix-B* and 10 mcg per dose with *Recombivax-HB*, but note that some experts recommend using the 40 mcg dose with either vaccine (Figure 5). In a randomized trial, investigators reported HIV-infected persons had better serologic responses when given 4 intramuscular 40 mcg doses of hepatitis B vaccine than 3 intramuscular 20 mcg doses [28]. Suboptimal responses to hepatitis B vaccine occur more frequently in HIV-infected persons when compared with HIV-negative controls. Accordingly, the ACIP recommends testing HIV-infected persons for antibody to hepatitis B surface antigen (anti-HBs) 1 to 2 months after completing the final dose of the vaccine series, with a titer of at least

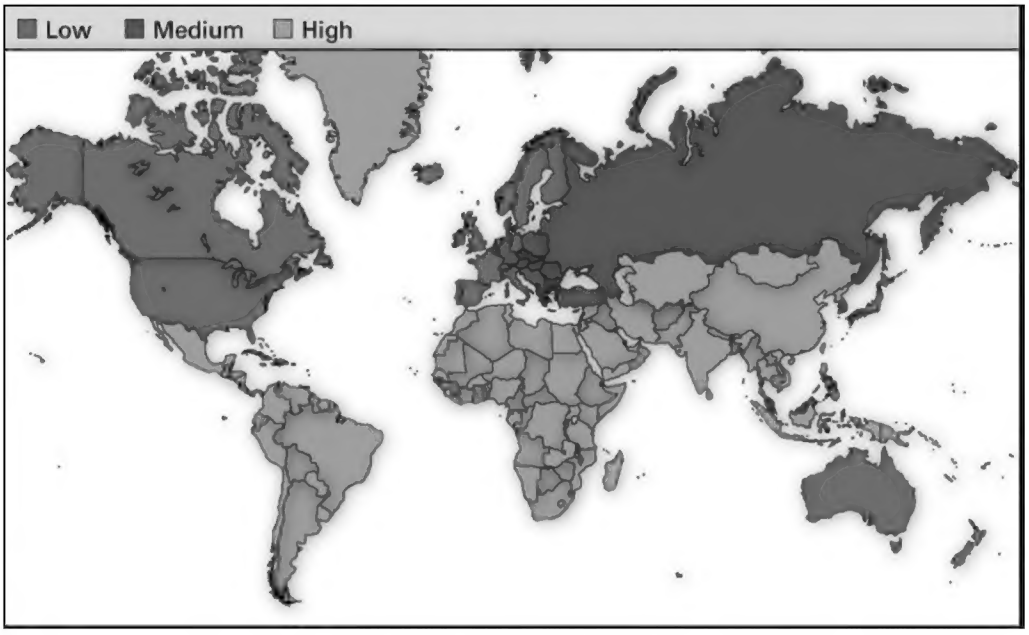


Figure 3. Geographic distribution of hepatitis A virus endemicity.

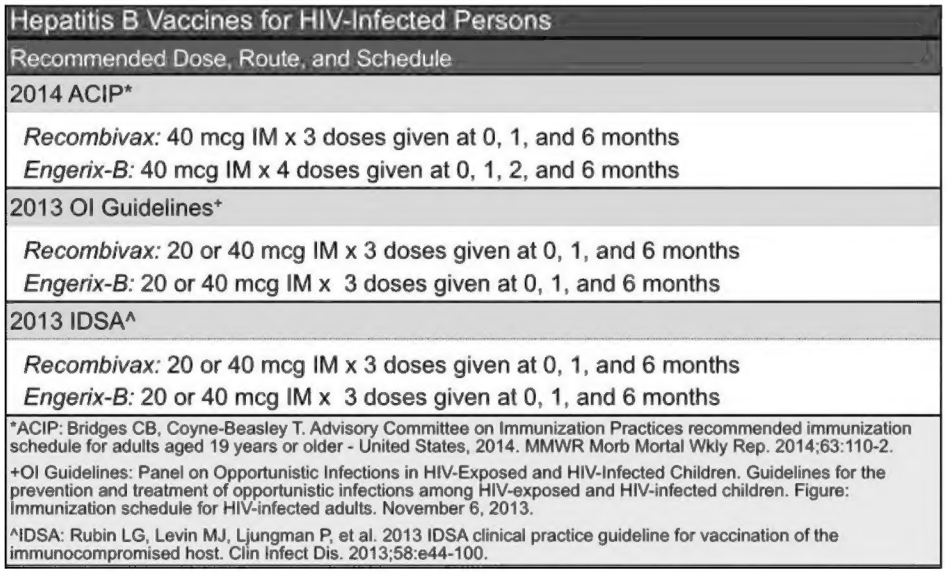
Hepatitis A Vaccine	Dose and Route
Havrix	1440 EL.U. IM x 2 doses given at 0, 6-12 months
Vaqta	50 U IM x 2 doses given at 0, 6-18 months
Notes: Vaccine indicated for HAV-susceptible patients with any of the following: chronic liver disease, injection-drug use, men who have sex with men, or persons with planned travel to countries that have high or intermediate endemicity for hepatitis A virus Certain specialists might delay vaccination until CD4+ count >200 cells/mm^3	

Figure 4. Recommended hepatitis A virus vaccine dosage and schedules for HIV-infected adults.

10 mIU/ml considered protective. The need for booster doses in HIV-infected persons has not been determined, but existing guidelines do not recommend routinely giving booster doses. Patients with an inadequate response to hepatitis B vaccine should receive three additional vaccine doses and be tested again 1 to 2 months after completing the final dose of the repeat vaccine series for serologic response to the vaccine. If the HIV-infected person has not responded to a total of 6 doses of hepatitis B virus vaccine, they are unlikely to respond to further doses.

Measles, mumps, and rubella vaccine

Although measles, mumps, and rubella (MMR) vaccine (*M-M-RII*) is a live attenuated vaccine, it is recommended for HIV-infected adults with a CD4 of at least 200 cells/mm who lack evidence



Hepatitis B Vaccines for HIV-Infected Persons
Recommended Dose, Route, and Schedule
2014 ACIP*
Recombivax: 40 mcg IM x 3 doses given at 0, 1, and 6 months *Engerix-B:* 40 mcg IM x 4 doses given at 0, 1, 2, and 6 months
2013 OI Guidelines+
Recombivax: 20 or 40 mcg IM x 3 doses given at 0, 1, and 6 months *Engerix-B:* 20 or 40 mcg IM x 3 doses given at 0, 1, and 6 months
2013 IDSA^
Recombivax: 20 or 40 mcg IM x 3 doses given at 0, 1, and 6 months *Engerix-B:* 20 or 40 mcg IM x 3 doses given at 0, 1, and 6 months

*ACIP: Bridges CB, Coyne-Beasley T. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2014. MMWR Morb Mortal Wkly Rep. 2014;63:110-2.

+OI Guidelines: Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Figure: Immunization schedule for HIV-infected adults. November 6, 2013.

^IDSA: Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2013;58:e44-100.

Figure 5. Recommended hepatitis B virus vaccine dosage and schedules for HIV-infected adults.

of immunity to measles [29]. The MMR vaccine is contraindicated for HIV-infected adults with a CD4 count less than 200 cells/mm. In order to minimize the risk of exposure of HIV-infected persons to measles, mumps, and rubella, susceptible close contacts should be vaccinated with MMR. In the general adult population, the MMR vaccine is indicated for adults born after 1956 without documented evidence of immunity to measles or rubella or prior immunization. A single dose of measles vaccine results in protective immunity in 95% of persons. A second dose of MMR is recommended for adults who: (i) were recently exposed to measles in an outbreak setting, (ii) were previously vaccinated with killed measles virus vaccine, (iii) were vaccinated with an unknown vaccine during 1963 to 1967, (iv) are students in post-secondary educational institutions; (v) work in health-care facilities, and/or (vi) plan to travel internationally. The MMR vaccine is contraindicated during pregnancy, and pregnancy should be avoided for 28 days after vaccination to minimize the theoretical risk of congenital rubella syndrome.

Varicella vaccine and zoster vaccine

Varicella vaccine (*Varivax*) is a live, attenuated vaccine that previously was contraindicated for all HIV-infected adults, regardless of their stage of HIV disease. If given, two doses of the varicella vaccine should be given 3 months apart [30]. For HIV-infected adults who have a CD4 count less than 200 cells the varicella vaccine is contraindicated. The herpes zoster vaccine (Zostavax) is also a live vaccine and it contains very high titers of varicella virus; this vaccine is contraindicated for HIV-infected adults who have a CD4 count less than 200 cells and could be particularly dangerous if mistakenly given as the varicella vaccine to an individual without immunity to varicella-zoster virus. For those patients who have a CD4 count of at least 200 cells, the 2015 ACIP recommendations do not advise for or against giving the zoster vaccine. In ACTG trial 5247, HIV-infected persons with a CD4 count of at least 200 cells received 2 doses of herpes zoster vaccine 6 weeks apart and the vaccine appeared to be safe and immunogenic [31].

Human papillomavirus vaccine

The US FDA has approved three human papillomavirus (HPV) vaccines: HPV-4 quadrivalent that comprises types 6, 11, 16, and 18 vaccine (*Gardasil*) in June 2006, HPV-2 that comprises types 16 and 18 (*Cervarix*) in October 2009, and more recently, in December 2014, the HPV-9

(*Gardasil 9*) that expands the serotypes for cancer protection (types 6, 18, 31, 33, 45, 52, and 58) and still has types 6, and 11 for prevention of genital warts [32, 33, 34]. These vaccines require 3 doses, given at 0, 2, and 6 months, and are recommended routinely for females at age 11 to 12 and for females aged 13 to 26 who have not previously received this vaccine or have not completed the full series. Ideally, females should receive this vaccine prior to becoming sexually active. In addition, the HPV-4 vaccine is approved for boys aged 13 to 26 and the HPV-9 for boys 9 through age 15. The HPV vaccines are considered safe for immunocompromised individuals since they are prepared from recombinant L1 capsid protein of HPV and thus are not live vaccines. Patients with low CD4 cell counts may have diminished immune responses to the HPV vaccines. There are no recommendations for the use of the HPV vaccine in men or in women older than 26. The HPV vaccine should not be given to pregnant women.

Poliovirus vaccine

In the United States, routine use of live oral polio vaccine was discontinued in 1999 [35] and the inactivated poliovirus vaccine (IPOL) is now the routinely administered vaccine. Routine polio vaccination of adults in the United States is not recommended, but may be indicated in travellers. For those unvaccinated HIV-infected adults who require polio vaccine, they should receive 3 doses of inactivated poliovirus vaccine, with the first 2 doses given 4 to 8 weeks apart and the third dose given 6 to 12 months after the second dose. Live oral poliovirus vaccine is contraindicated in HIV-infected persons and their household contacts, regardless of the HIV-infected person's immune status.

Smallpox vaccine

The current commercially available smallpox vaccine (*Dryvax*) consists of live vaccinia virus (a virus similar to smallpox virus) and this vaccine is contraindicated in all HIV-infected persons if used as part of a pre-event program, mainly because of the increased risk for progressive vaccinia among persons with HIV infection [36]. There are limited data regarding the risk of smallpox vaccination for HIV-infected persons, mainly because the routine use of smallpox vaccination for the civilian population had ceased prior to the HIV epidemic. Smallpox vaccination for the military, however, has overlapped with the HIV epidemic. In 1989, a case report described an HIV-infected military recruit who received smallpox vaccination and developed disseminated vaccinia and was successfully treated with vaccinia immune globulin [37]. In the event of a bioterrorism attack involving smallpox, vaccination of potentially exposed HIV-infected individuals would be considered despite the risks of the vaccine.

Vaccines related to travel

Vaccines related to travel are generally not part of the initial evaluation process of HIV-infected persons. Nevertheless, many HIV-infected persons will eventually travel to regions of the world that require multiple preventive vaccinations against typhoid fever, cholera, yellow fever virus, Japanese encephalitis virus, and rabies virus. Recommendations for appropriate travel-related vaccines can be very complex and depend on numerous factors, including the HIV-infected person's immune status, the specific region of travel, and the types of exposure likely to occur in that region [38]. Accordingly, we recommend that HIV-infected persons who will travel undergo an evaluation by a medical provider who has expertise in travel-related issues and that this travel evaluation occur well in advance of the travel date to allow time for all appropriate immunizations to be given. The Centers for Disease Control and Prevention (CDC) provides an on-line resource for general information regarding HIV and travel [39, 40].

CONCLUSION

Vaccinations are a sometimes overlooked, but critical, component of the care of HIV-infected adults. HIV care providers must ensure vaccine coverage among their patients, with vaccinations ideally administered shortly after early HIV diagnosis and before loss of immune responsiveness. Patients with severe immune degradation (e.g., CD4 <200 cells/mm^3) are at the highest risk for vaccine-preventable diseases, but unfortunately have the poorest responses to vaccinations. Whether to vaccinate patients with low CD4 counts at

presentation or wait for some degree of immune restoration after starting CART remains an important question. More immunogenic vaccines as well as studies to define the optimal timing for vaccination among those with advanced disease are needed.

CONFLICT OF INTEREST STATEMENT

This paper does not have any conflict of interests.

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